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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,399	11/17/2003	Peng Cho Tang	034536-0893	2032

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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 04/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/714,399	TANG ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *2-13 and 15-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/16/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to an election filed on 2/3/06. There are twenty-one claims pending and two under consideration. Claim 1 is a compound claim. Claim 14 is a composition claim. This is the first action on the merits. The application concerns some 7,8-dihydro-6H-cyclopenta[g]quinoxaline and 6H-cyclopenta[g]quinoxaline compounds and compositions.

Election/Restrictions

2. In the restriction mailed on 1/4/06, the Examiner indicated that claims 2-6 and 7-13 read upon Group III. Claims 2-6 require atoms A and D both to be nitrogen. Claims 7-13 require atom A to be nitrogen and atom D to be sulfur. As such, claims 2-13 read upon Groups I and IV but not upon Group III. The Examiner regrets the error.

3. Applicant's election without traverse of Group III, the compounds and compositions with A = B = D = carbon in the reply filed on 2/3/06 is acknowledged.

4. Claims 2-13 and 15-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 2/3/06.

Title

5. The title of the invention is no longer descriptive after restriction. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: replacing the phrase "Tricyclic Quinoxaline" by the phrase, "Cyclopenta[g]quinoxaline".

Abstract

6. Applicant is reminded of the proper content of an abstract of the disclosure. A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details. The abstract is too short and generic. Examiner suggests claim 1, lines 1-7 including the figure, and the utility.

Priority

7. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. [1] as follows: the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the

later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, provisional Application No. 60/059,686, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The proviso in lines 16 and 17, page 127 lacks support. Nowhere in the specification of provisional Application No. 60/059,686 is such a relationship linking the description among radicals R^5 and R^6 described. Such a negative limitation is a new concept and requires description. In *Ex parte Grasselli, et al.* 231 USPQ 393, decided June 30, 1983, the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences said: "we agree with the examiner's position of record that the negative limitations recited in the present claims, which did not appear in the specification as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112." "It might be added that the express exclusion of certain elements implies the permissible inclusion of all other elements not so expressly excluded. This clearly illustrates that such negative limitations do, in fact, introduce new concepts."

Thus, the effective filing date of the present claims is 8/4/98, the filing date of the grandparent application 09/129,139.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The statement in lines concerning the double bonds 10-11 of claim 1 is confusing with the present all carbon election for two reasons. Firstly, is the double bond signified by one of the dotted lines optional or mandatory? On page 12 there are drawings of nine preferred formulas. All of these have a double bond in the five-membered fused ring but none of these concern the present cyclopenta[g]quinoxaline compounds. For the search, the Examiner assumed the double bond is optional.

9. Secondly, A, B, and D, must be "carbon". Carbon is a tetravalent atom. When there is a double bond between atoms B and D, there must be a single bond between atoms B and A. Radical R^1 is attached to one of the four valences of A, What is attached to the fourth valence? Is it a hydrogen atom or could it be something else?

10. Claims 1 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. There is no definition for variables R^1-R^3 in the claims. The definition in lines 1-6, of page 127 does not apply to the present all carbon case, when none of A, B, or D is nitrogen.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making prodrugs of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The [eight] factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146

USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the prodrugs is found in line 3, page 45, which merely states Applicants intents to make such derivatives. No structures of any such prodrug are suggested. c) There is no working example of a prodrug of a compound the formula of claim 1. d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. The table on

the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the millions of thousands of compounds of formula of claim 1 as well as the presently unknown list of potential prodrug derivatives embraced by claim 1.

MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug.

The Examiner suggests deleting the phrase "or a prodrug" from claim 1.

12. Claims 1 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for making the compounds of the formula of claim 1 with A = B = D = carbon. The specification does not enable any skilled process chemist or pilot-plant operator to make the invention commensurate in scope with these claims. The eight factors to be considered in making an enablement rejection have been summarized above. The three important factors leading to such a conclusion are the lack of guidance in the specification, the lack of any working example of the presently claimed compounds, and the state of the art in making the presently claimed compounds.

a) Preparing the claimed compounds with A = B = D = carbon would require developing a new synthesis. Considering the large number of compounds to be made, this is a large quantity of experimentation. b) The direction concerning making the claimed compounds is found in lines 17-21, page 55. This passage says, "[t]he compounds of this invention may be readily synthesized using techniques well known in the chemical arts. Other synthetic pathways for forming the compounds of the invention will be apparent to those skilled in the art and are deemed to be within the scope and spirit of this invention." No other guidance is provided. Since cyclopenta[g]quinoxaline compounds, *i.e.* compounds with A = B = D = carbon and a double bond in the five-membered ring are unknown to the chemical arts, techniques for making them cannot be, "well known in the chemical arts".

c) There is no working example of a compound of formula of claim 1 with A = B = D = carbon. d) The nature of the invention is chemical synthesis, which involves chemical reactions. e) The state of the art, as mentioned above, is not even the simplest compound with A = B = D = carbon and a double bond in the five-membered ring has ever been made. The ring system is unknown to chemical science. f) The artisan using Applicants invention to prepare the claimed compounds would be a process chemist or pilot plant operator with a BS degree in

chemistry and several years of experience. He would know how to make known ring systems by looking up their synthesis in the literature but be unaware of how to make unknown ones. g) Chemical reactions are well-known to be unpredictable, *In re Marzocchi*, 169 USPQ 367, *In re Fisher*, 166 USPQ 18. h) The breadth of the claims includes all of the millions of compounds of the formula of claim 1. Thus, the claims are broad.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

13. Claims 1 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement for using the compounds of the formula of claim 1 with A = B = D = carbon. The specification is not adequately enabled for the scope of fused rings that have a carbon atom at position A and differing ring saturations. The specification does not enable any skilled pharmacologist or physician to use the invention commensurate in scope with these

claims. The eight factors to be considered in making an enablement rejection have been summarized above.

a) Determining if any particular claimed compounds with A = B = D = carbon would be active would require synthesis of the substrate and subjecting it to testing with Applicants' PDGFR, FLK, and EGFR enzyme inhibition assays. Considering the large number of compounds to be made this is a large quantity of experimentation. b) The direction concerning the claimed compounds is found in lines 19-22, page 10, which merely states Applicants intent to make and use such compounds. These compounds are restricted to ones "known in the chemical arts". As mentioned above, cyclopenta[g]quinoxaline compounds are not known in the chemical arts".

c) In the instant case none of the examples contains A = B = D = carbon. None of these examples contain A = carbon. Only two, compounds No. 242 and 270 have B = D = carbon. These two have A = nitrogen and appear to be prophetic since no physical data are listed for examples 242 and 270. Only Examples 1-4 appear to be working examples. Examples 1-4 are benzimidazoles with A = D = nitrogen and B = carbon. These is biological data on only two compounds listed on page 124 of the specification. Both compounds are also imidazoles but it is

unclear to the Examiner where these two compounds came from since their synthesis is not reported in the specification or in any of the tables on pages 21-37.

d) The nature of the invention is inhibition of PDGFR, FLK, and EGFR enzyme and treatment of human diseases with Applicants' compounds. This involves physiological activity. The nature of the invention requires an understanding of the PDGFR, FLK, and EGFR enzymes, the binding activity of small ligands to those enzymes, and the ability of those compounds to inhibit PDGFR, FLK, and EGFR enzyme. In view of the unpredictability of enzyme binding activity and claimed divergent atoms with varied polarity, size, and polarisability, the skilled physician would indeed question the inclusion of such all carbon rings, commensurate in scope with these claims. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

e) The state of the art is detailed knowledge of the PDGFR, FLK, and EGFR enzymes is lacking. The structural requirements of ligands to this receptor are poorly understood. The five-membered imidazole ring of Applicants' working examples benzimidazole compounds is strongly basic. The cyclopentene and cyclopentadiene rings of the rejected compounds are non-basic. In fact the cyclopentadiene ring is slightly acidic. The imidazole ring of the working

examples is a hydrogen bond acceptor. The cyclopentene and cyclopentadiene rings of the rejected compounds are not. The imidazole ring of Applicants working examples is aromatic and π-electron rich. The cyclopentene and cyclopentadiene rings of the rejected compounds are neither. There is no reasonable basis for the assumption that the all carbon compounds embraced the present formula of claim 1 will all share the same biological properties with the imidazole compounds made and tested. There is no basis in the prior art for assuming in the non-predictable art of enzymology that structurally dissimilar compounds will have such activity, *In re Surrey* 151 USPQ 724.

Replacing one atom by another in a biologically active ring compound is called bioisosteric replacement. Olesen (Curr. Opin. Med. Chem.) provides the state of the art in this field. Olesen (Curr. Opin. Med. Chem.) states in the last complete paragraph, page 1, that, "replacement of a heterocyclic or carbocyclic ring with another heterocyclic ring is probably the most widespread method for a bioisosteric transformation used by medicinal chemists." In the paragraph spanning pages 5 to 6 the references states, "[o]ne of the major drawbacks associated with the use of bioisosteres is the lack of generality when transferring a certain type of bioisosteric transformation between lead compounds for different therapeutic targets. This failure arises since applying a bioisosteric replacement in

the lead compound almost always has an impact on a number of physicochemical properties of the compound, e.g., the number of hydrogen donors or acceptors, logP or pK_a . The bioisosteric replacement may also give too much steric bulk or induce an unfavorable conformation in the molecule. Each of these changes can be detrimental for the compound's interaction with the target molecule and the number of changes that can be tolerated is not always clear at the initial stage of the lead compound optimization process."

Lima (Curr. Med. Chem.) states in the first sentence, first paragraph, second column, page 31, "[r]ing bioisosterism, is undoubtedly the most frequent relationship in drugs of different therapeutic classes". The reference states in the first complete paragraph, page 27, "*[h]owever, bioisosteric replacement which successfully occurs in a series of compounds acting as* [sic] *a type of bioreceptor, will not necessarily be successful in another therapeutic series, acting through other receptors* [emphasis in original]".

Prisinzano (Med. Chem. of CNS Active Agents) in the first paragraph, page 35, "[i]t is difficult to relate biological properties to physicochemical properties of individual atoms, functional groups or entire molecules because many physical and chemical parameters are involved simultaneously and are therefore difficult to quantitate. Simple relationships as described above often do not hold tip across the

many types of biological systems seen with medicinal agents. That is, what may work as an isosteric replacement in one biological system (or a given drug receptor) may not in another."

Wolff (Burger's Medicinal Chemistry) says in the paragraph spanning pages 787 to 788, "fundamental chemical and physical changes will result from [bioisosteric replacement] which may in themselves profoundly affect the pharmacological action of the resulting molecules. ... The effect and pharmacological significance of many of these parameters are unpredictable and must be determined experimentally".

Applicants urge the equivalence of oxygen and carbon (CH_2) in transforming their lone isoxazole example, compound No. 240 into the claimed cyclopenta[g]quinoxaline compounds. Wermuth (The Practice of Medicinal Chemistry) writes in the last paragraph on page 228, "the O $\leftrightarrow$ CH_2 isosterism very often yields anomalous results".

f) The artisan using Applicants invention to treat diseases with the claimed compounds would be a physician with a MD degree and several years of experience. He would be unaware of how to predict *a priori* how a changing a heterocyclic ring would affect biological activity. In view of the divergent rings with varied basicity and polarisability, the skilled physician would indeed question

the inclusion of such fused rings, commensurate in scope with these claims. g) Physiological activity, is well-known to be unpredictable, *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). The art recognized of lack of predictability in the art of bioisosteric replacement was discussed above.

h) The breadth of the claims includes all of millions of compounds of formula of claim 1. Thus, the scope is very broad. The present claims embrace two cyclic rings, which are not art-recognized as equivalent to the heteroaryl rings made. The specific compounds made are not adequately representative of the compounds embraced by the extensive Markush groups instantly claimed.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed.

Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

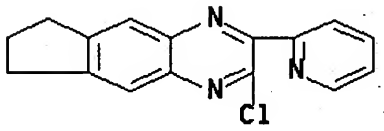
Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Cai ('373). The compound shown below fits the formula of claim 1 with $R^1 = R^2 = R^3 = R^7 = H$, $R^5 = R^6 =$ hydroxy, $R^4 =$ nitro, A = B = D = carbon, and single bonds between atoms A, B, and D. It has Registry Number 170099-39-5 and is found in Table II, line 37, column 29 of the reference. It is the eighth compound from the bottom of the Table. A second anticipatory compound is found in line 38, column 29, Table II. The compounds have been drawn by Chemical Abstracts in the tautomeric keto form. Compositions of the compounds are taught in lines 23-37, column 43. Thus, the present claim 14 is anticipated.

15. Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by Carson ('499). The compound shown below fits the formula of claim 1 with $R^1 = R^2 = R^3 = R^4 = R^7 = H$, R^5 = 2-pyridyl, R^6 = chloro, A = B = D = carbon, and single bonds between atoms A, B, and D. It has Registry Number 239095-96-6 and is found in lines 13-21, column 88 of the reference. A second anticipatory compound is found in lines 3-12, column 88.



Conclusion

16. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please

direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

17. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (571) 273-8300. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 9:00am to 5:30pm, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, SPE of Art Unit 1624, at (571)-272-0661.

Thomas C. McKenzie, Ph.D.
Primary Examiner
Art Unit 1624
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TCMcK/me